AMPK-glycogen interplay: an opportunity for drug design

Valorization

Beyond the scientific relevance of the thesis issued herein, the presented work describes an area of research that could be translated into a socially and economically relevant product. In **Chapter 5**, the disclosed cluster of small, drug-like molecules which act on the energy sensor AMPK could lead in the future to a new drug of interest in a number of diseases.

A new drug to target AMPK in an innovative manner

Relevance & Target groups

As described in **Chapter 2**, AMPK is involved in a wide number of diseases, from cardiac diseases to cancer through diabetes. Over the years, this protein has emerged as a potential drug target in many of these fields and the area of research keeps expanding as novel AMPK downstream effects unravel. The most established domain in which AMPK beneficial targeting is known is type 2 diabetes. In contrast to type 1 diabetes, type 2 diabetes is associated to obesity, physical inactivity, poor diet and age. Due to the change in lifestyle induced by worldwide economic development, more and more people are at risk of developing this condition [1]. According to the most recent estimations of the International Diabetes Federation, 382 millions of people suffer from diabetes worldwide and this number is predicted to have risen by 55% in 2035 if trends keep as they are. Beyond the direct risk associated with the disease, diabetes leads to many more health complications such as cardiovascular diseases and kidney failure. Logically, the costs in healthcare created by diabetes are enormous: as a consequence of undiagnosed diabetes alone, the healthcare costs in the USA were estimated to USD 18 billion for one year [1].

If only for its beneficial role in treatment of this metabolic disorder, AMPK is therefore well worth studying. Moreover, in the past decades, a few proteins in specific cellular pathways have emerged as responsible for age-related disease occurrence [2, 3]. To clarify, the mutation of these proteins in animal models can prolong their healthy lifespan significantly. For some of these targets such as those related to insulin/IGF1, certain mutations correlate with longevity in different human cohorts [2]. Although AMPK did not yet reach such a level of characterization, there is evidence to show that AMPK activation may also potentiate an increase of healthy lifespan [3].

Even though AMPK is involved in many pathways, studies using indirect or direct activators showed mostly beneficial effects without side-effects in a wide array of diseases [4]. Only in very specific cases of the fields of cancer and neurodegenerative disorders, the activation of AMPK sometimes led to worsening of the symptoms. Therefore, the targeting of AMPK is considered as generally safe with only cautions to

be taken under some conditions.

In summary, considering the high occurrence of diseases related to ageing or "modern" lifestyle that could benefit from AMPK activity, the development of bioactive compounds that target AMPK is of obvious relevance, both from social and economic points of view.

Product & Innovation

Several methods to directly or indirectly activate AMPK with drug-like molecules have been described [5]. For direct targeting, three different methods exist that activate the protein through action on different aspects of AMPK regulation. In each of these categories, a high number of studies have led to the identification of many compounds with different structures. Unfortunately, to date, none of these molecules have reached the market, generally due to off-target effects or to poor absorption in the body. With regards to indirect activation of AMPK, different types of molecules mimic an energy stress within the cell they reach, thereby activating AMPK. Among these, several natural products and nutraceuticals, such as resveratrol or curcumin, were shown to activate AMPK [6]. More importantly, the most widely prescribed drug, metformin, also activates AMPK in an indirect manner [7]. This treatment against type 2 diabetes exerts its beneficial effects partly through AMPK. However this drug as well as all indirect AMPK activators has many other targets than AMPK. Therefore the search for a safe and efficient strategy to directly target the protein is still on-going.

In **Chapter 5**, we describe the identification of novel molecules that target AMPK in an innovative manner. Our primary aim in designing these compounds was not to directly modulate AMPK activity but rather AMPK effects: instead of influencing AMPK activity as other AMPK activators do, our compounds were selected for their ability to modify AMPK localization within the cell, and bring it away from the cellular store of glucose, glycogen. This change of localization should influence the protein partners that AMPK can find and thereby alters the outcome of AMPK activity. Unexpectedly, the compound, named 6469172, which had the strongest ability to change AMPK localization, also modulates AMPK activity. The precise mechanism that triggers this increase in activity is still unexplained at this stage, but still provoked glucose uptake in cells treated with 6469172. Therefore this compound shows promises for the treatment of type 2 diabetes where glucose needs to be taken up from the blood into cellular reserves.

In summary, the newly identified compound, 6469172, is the basis on which a new drug targeting AMPK could be developed. The mechanism of action which targets AMPK localization rather than directly its activity makes it an innovation in the field of AMPK targeting. Considering on one hand the interest that AMPK activators trigger for

their beneficial roles in many diseases and on the other hand the current lack of an efficient strategy to take advantage of AMPK effects, the compound 6469172 shows interesting potential for further development into a marketed product.

Schedule & Implementation

Despite its great interest for future applications, the compound 6469172 is still in a very early stage of a drug development. The data presented within this thesis establish the ability of 6469172 to change AMPK localization and to bind directly to one of the domain of this protein. Furthermore, the first tests show the change of AMPK activity induced by treatment with 6469172 and the resulting increase in glucose and fatty acid uptake. Although these data are encouraging, they are far from sufficient. As explained in **Chapter 6**, even though bioinformatics tools were used to filter out molecules that were unlikely to behave as drugs, many tests still need to be conducted to certify that our newly-found molecule meets the requirements regarding absorption, distribution, metabolism and excretion (ADME) once in the body [8]. Strict criteria regarding toxicity have also to be adhered to. Moreover, further levels of characterization, both *in vivo* and *in vitro*, have to be followed to assess the benefits that this molecule can trigger in disease conditions. Finally, the compound 6469172 together with other structurally-related ones identified herein will serve to document structure-activity relationship studies, which will lead to the definition of another chemical structure with optimal characteristics in both ADME/toxicity and potency tests. This development phase is called hit-to-lead and is followed by lead optimization. After these stages, the final compounds enter clinical trials, which is again a very long and costly process.

Therefore, a long road still awaits 6469172 before the concept developed with this molecule can be translated into a commercial product. Generally, from the initial idea to the market launch, the development of a drug takes 12-15 years and costs more than one billion USD [8]. Our initial work brought us from initial idea to the beginning of the hit-to-lead phase, but the main costs remain ahead with the clinical trials to come. Even though the phases of early drug development are progressively taken over by academic groups or academic drug development centers, clinical trials remains the exclusive field of established pharmaceutical companies or their spin-off. In the case of 6469172, no patents were filled at this stage because the gathered data were considered to provide too little ground for a university to take the financial risk. However, discussions with pharmaceutical companies are planned to see how research could be carried on possibly with other undisclosed molecules.

In summary, the newly-identified compounds presented herein have some promising and innovative application lying ahead, even though the stage of development and characterization is still too early to really predict whether a commercial application could stem from them.

References

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